ORIGINAL

November 30, 2005

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket 2005P-0121

Amendment to RS Medical's Petition for the Reclassification of the Non-invasive Bone Growth Stimulator

Dear Sir or Madam:

This document amends RS Medical's petition for the reclassification of the Non-invasive Bone Growth Stimulator referenced above. It responds to the points to consider that were forwarded to RS Medical on July 27, 2005, via email, by the Food and Drug Administration's (FDA's) review staff. These same FDA comments were forwarded to RS Medical by Donna-Bea Tillman, Ph.D., Director of the Office of Device Evaluation, in her letter of August 12, 2005.

RS Medical is also aware that comments related to its petition have been submitted to FDA's Dockets Management Branch by various third parties. These comments will not be addressed in any specific order, or in their entirety, in this amendment; but RS Medical may provide an assessment of all these comments at a later date. Notwithstanding this, the responses to the FDA-points will sometimes include observations about certain aspects of the comments made by third parties when those comments relate to the points raised by FDA.

The FDA points to consider follow in italic; our responses follow:

1. In support of this petition, the sponsor has provided "new information", as described within § 513(e) - "publicly available, valid scientific evidence", which includes the following (42 Literature articles listed within Appendix A):

a. sham-controlled, double-blinded, prospective studies,
b. standard-of-care controlled (non-sham), prospective studies,
c. historic-controlled, retrospective studies, and
d. non-controlled studies.

These articles appear to differ considerably in respect to study size, drop-out rates, clinical/imaging evaluation, prior treatment, site of treatment, concurrent treatment, and etc. The petition does not appear to include an analysis of these disparate study parameters and their affect on the validity of the scientific evidence. The petition should be revised to include [a] rationale for consolidating the provid[ed] literature studies as

scientific evidence considering the studies inconsistencies. In addition, the petition does not appear to include literature articles which may be unfavorable to the petition. Additional research may be necessary to verify that the submitted summary literature is an adequate sample of the available scientific evidence and includes scientific evidence which may not support this petition.

Response: There are multiple components to consider in this point.

First, the Agency notes:

> *In support of this petition, the sponsor has provided "new information", as described within § 513(e) - "publicly available, valid scientific evidence", which includes the following (42 Literature articles listed within Appendix A)*

Actually, the petition provided more than 42 literature articles regarding clinical studies for the type of device.

RS Medical identified 41 articles based on its key-word literature search (see Attachment 1), which focused on clinical trials. Then, to help ensure that the petition contained all appropriate information, RS Medical reviewed both the Summaries of Safety and Effectiveness for the approved devices, and their labeling, to identify any additional articles that might be of interest. An additional 15 articles resulted from this review. (In general, these 15 articles were not identified in the literature search because they were not predominately about clinical trials.) Thus, the petition described in some detail a total of 56 articles.

The Agency goes on to note:

> *...articles appear to differ considerably in respect to study size, drop-out rates, clinical/imaging evaluation, prior treatment, site of treatment, concurrent treatment, and etc. The petition does not appear to include an analysis of these disparate study parameters and their affect on the validity of the scientific evidence. The petition should be revised to include [a] rationale for consolidating the provid[ed] literature studies as scientific evidence considering the studies inconsistencies.*

The articles cited in the petition resulted from research conducted by different investigators, at different times, and in different institutions; the studies varied in certain approaches. Notwithstanding this, the petition identified certain study factors for each study in order to better understand how the studies compared with one another. For example, for capacitive coupling (CC) and pulsed electromagnetic field (PEMF) devices used **in nonunion fractures**, the petition identified, among other things:

- type of study (e.g., prospective, randomized, retrospective);
- control group;

- the fracture site;
- length of follow-up;
- number of subjects;
- number of subjects with previous treatment;
- number of subjects with concomitant surgery;
- number of subjects with sham controls;
- the manufacturer of the device;
- the output waveform;
- treatment regimen;
- time between fracture and stimulation treatment;
- radiological definitions of union;
- clinical definition of union; and,
- rates of success.

There were instances, of course, when some of these factors could not be identified in a particular article, but in general they were. The petition provided similar information for the CC and PEMF devices **when used for fusion**.

This work was done to determine if there were some studies with so little information about study parameters that they should be disqualified from consideration. As it turned out, none of the articles were disqualified for this reason. This work also provided an opportunity to determine if any study exhibited some internal inconsistency worthy of note, e.g., the number of subjects entered could be compared with the number of subjects followed to determine if there was a discrepancy. RS Medical noted some inconsistencies in certain studies, as footnoted on the tables in the petition. It also allowed RS Medical to see if there were certain uses, for example, uses in certain locations in the body, where the devices seemed less effective than in other locations. There is no significant indication that the device would be ineffective for any specific anatomical location.[1] Thus, the petitioner

[1] Several articles identified a lower union rate for the humerus, but the sample sizes were small (Cheng/1985, 2/8; Heckman/1981, 4/9). In one small study the investigator notes that fragment mobility is often a problem (Marcer/1984, 5/13). Bassett reports in 1982 6/8 successes, and also in 1982 70% to 80% successes in 52 subjects in the humerus; he notes that variation in success is attributable to variations in immobilization. Hinsenkamp/1985 had 19 subjects with 14 successes (73.7%).

utilized a planned and careful approach to the assessment of the related literature, to the extent that a literature review allows.

There is, of course, certain information that might be critical for supporting the approval of a premarket approval application (PMA) that is not available from each article, or perhaps from any article. For example, there is sometimes no specific information about how the serial radiographs were evaluated by an investigator to conclude that fusion, or union, had, or had not, occurred. The petition, however, is not seeking a PMA approval for any specific device; it is seeking reclassification for a type of device. The petition need not show that each device included within the type of device is safe and effective or that any one of the devices is safe and effective, at least as would be done in a PMA. The petition must show that the devices within the type can be made to be safe and effective in the proposed new regulatory class through the application of the controls available to that class; and, the petition should offer enough evidence related to the safety and effectiveness of the existing devices within the type in order for those devices to serve as predicate devices for new devices within the type.

This requires a reasonable body of valid scientific evidence. But, what would be a deficiency in evidence submitted in a PMA, is not necessarily a deficiency in a reclassification petition. Evidence derived from different devices within the type can legitimately support the petition when such evidence might not support a PMA for any one device within the type. Also, the studies themselves need not employ the same set of procedures and evaluation criteria that are normally employed in PMA-related studies. A failure to do so for a specific device that is the subject of a PMA confounds the analysis of safety and effectiveness data for the specific device. But, when literature articles describe numerous studies conducted under somewhat differing circumstances, using different devices within the type, and all the studies conclude that the device which was used performed safely and effectively, such literature provides compelling evidence that **the type of device** can be safe and effective.

Seeing similar results from somewhat different study approaches reinforces, rather than calling into question, the conclusion that the Non-Invasive Bone Growth Stimulator can be a safe and effective **type of device**.

To this point, the clinical studies reported in the literature demonstrate that the Non-invasive Bone Growth Stimulator facilitates osteogenesis and promotes bone growth at fracture sites created by trauma (either accidental or surgical in nature) through the application of electrical and/or magnetic fields. Over 6,500 subjects[2] have been evaluated in 41 clinical studies with 28 (68.3%)[3] of these studies being prospective in nature.

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[2] This number is less than the originally reported 6,700 subjects (see page 0014 of the petition), as the findings from the study using the combined magnetic field device are not being included in this response.

[3] The number of clinical studies (41) and prospective studies (28) reported in this response are less than the numbers originally reported (see page 0014 of the petition), as the findings from the study using the combined magnetic field device are not included.

The results from 33 prospective and retrospective studies involving over 5,600 subjects and included in the original petition demonstrate that the Non-invasive Bone Growth Stimulator is an effective treatment for nonunion at a variety of fracture sites and locations, and for patients who have suffered long-term disability and for whom other treatments have not been successful.[4] The five clinical studies which investigated the safety and effectiveness of capacitive coupling for nonunion involved 351 subjects with 327 (93.2%) experiencing at least 1 surgical intervention prior to stimulation treatment.[5] The 28 studies for PEMF devices involved 5,318 subjects, the majority of whom failed at least one previous treatment. Both the capacitive coupling and PEMF devices were effective.[6] For capacitive coupling, the reported effectiveness rates ranged from 60-88%; for PEMF, the rates ranged from 50-100%. For both PEMF and capacitive coupling, the lower rate of the effectiveness ranges were estimated from randomized, double-blind clinical studies involving sham stimulation. But, these same studies estimated lower rates in the sham group as well. For example, Scott and King reported the results of a randomized, double-blind, sham-controlled study investigating the effectiveness of capacitive coupling for nonunion (1994). The union rate in the active group, however, was 60% compared to 0% in the sham stimulation group. Sharrard reported similar results in a randomized, double-blind, sham-controlled study of a PEMF device (1990). In this study, 50% of the subjects receiving PEMF stimulation achieved success compared to 8% in the sham stimulation group. Although the clinical studies did indeed vary in their definition of success and follow-up, the average overall success rate (radiographic and clinical success) for capacitive coupling was 77% and 76% for PEMF.

The results from 7 clinical studies involving 883 subjects, and included in the original petition, reported the effectiveness of the Non-invasive Bone Growth Stimulator as an adjunct to lumbar spinal fusion.[7] [8] Five of 7 of these studies compare study groups who received stimulation, to a control group who received surgery but not the post-operative stimulation regimen.[9] All 7 clinical studies reported an overall success rate, which considered both radiological and clinical success. The overall success rate reported for subjects receiving capacitive coupling as an adjunct to lumbar fusion was 85% compared to 65% of subjects who received sham stimulation. The overall success rate for PEMF devices ranged from 65-98% depending upon the study. The randomized, control clinical compared a PEMF device to a sham-control device and demonstrated an overall success rate of 92% in the PEMF stimulation group compared to 68% in the sham stimulation group.

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[4] See pages 0125 and 0126 of the original petition for a complete bibliography of these prospective and retrospective studies.
[5] See pages 0018 and 0025 of the original petition for overviews of these studies and descriptions of the study populations.
[6] See pages 0020 through 0022 and 0027 through 0034 of the original petition for overviews of these studies and descriptions of the study populations.
[7] The one clinical study involving 243 subjects which investigated the safety and effectiveness of a combined magnetic field device is eliminated from this summary.
[8] See page 0371 of the original petition for a complete bibliography of these studies.
[9] See page 0058 of the original petition for overviews of these studies.

The clinical studies cited in the original petition were published by a variety of authors in a number of different journals. These journals included well-recognized, peer-reviewed publications, such as the Journal of the American Medical Association, the Journal of Bone Joint and Surgery, Spine, and Orthopedics. These articles were also authored in many cases by well-recognized experts in their fields who are also associated with prominent universities.

A number of the articles provided enough detail to identify patient characteristics that may influence effectiveness, such as the space to be bridged in nonunion fractures, previous unsuccessful treatment with a Non-invasive Bone Growth Stimulator, and current smoking habits.

As noted above, the differences in the studies help support, not detract from the conclusion that the Non-invasive Bone Growth Stimulator can be a safe and effective **type of device**. In RS Medical's opinion, there is no need for additional evaluations of these studies, and there is certainly no reason to eliminate them from consideration because they exhibit differences and may not have all the detailed information required of a PMA study.

The Agency's point to consider also states:

> *In addition, the petition does not appear to include literature articles which may be unfavorable to the petition. Additional research may be necessary to verify that the submitted summary literature is an adequate sample of the available scientific evidence and includes scientific evidence which may not support this petition.*

As noted above, the petition explains how RS Medical identified the literature articles that were cited and included. We assume the Agency does not mean to suggest that RS Medical failed to adhere to the literature search methodology described in the petition, but is requesting that the search methodology be expanded. Thus, RS Medical has conducted a new search. In addition, RS Medical has reevaluated the search it has already performed to be certain that none of the software "screened" articles excluded from evaluation are pertinent to the petition.

Before describing the results, however, it is appropriate to consider the question of what information "*...may not support this petition.*"

Everyone knowledgeable in this field is fully aware that a device can be made to produce output parameters that are not safe or effective. Notwithstanding the obvious nature of this fact, the petition itself frequently notes that "unsafe or ineffective output parameters" is one of the risks of the device. Thus, preclinical or clinical studies which verify this fact **are not necessarily unfavorable** to the petition. Such studies **would be unfavorable** to the petition if they involved one of the specific devices proposed for reclassification. This is because the study would suggest that this specific device might be unsafe or ineffective, and should not serve as a predicate

device in Class II (even though it has been subjected to premarket approval). Preclinical and clinical studies in which there are unsuccessful outcomes **are not unfavorable** to the petition when the study involves a Non-invasive Bone Growth Stimulator that has not been included in the petition. Such studies only support the petition's assertion that a device can be made to produce output parameters that are not safe or effective.

RS Medical does not wish to belabor this point, but a number of the comments submitted in opposition to our petition are based upon a misunderstanding, or a misrepresentation, of what is pertinent to the approvability of the petition. The comments often cite factors that would be important in a PMA, but that are not necessarily important in a reclassification petition. Studies showing that a specific device produced unsafe or ineffective output parameters would be pertinent to a PMA for that specific device given that such facts would be pertinent to FDA's deliberations on the approvability of that device. But, such studies are not pertinent to the reclassification of the devices in this petition, unless the studies apply to a specific device proposed for reclassification.

Several comments from King & Spalding, LLP (K&S), and comments from at least two apparently interested persons, focused on this issue. In his June 28, 2005 testimonial (2005SP-0121 C1), Hansen Yuan, M.D., notes: "Research has shown that variations in the device's output can yield varying results, such as no clinical benefit at all." In her June 26, 2005 testimonial ((2005SP-0121 C3) Nicola Partridge, Ph.D., notes: "...research has shown that variations in the device's output can produce varying results including no clinical or preclinical benefit at all." (It is interesting that both comments employ remarkably similar language.)

RS Medical agrees with these observations. Furthermore, the observations are consistent with the petition. These observations, however, are not by themselves pertinent to the approvability of the reclassification action. The issue is whether ineffective output parameters can be identified prior to their marketing; and, such outputs can be avoided during product development, and if not, they can be identified prior to marketing based on testing requirements that can be imposed under the Class II regulatory controls.

K&S notes that "RS Medical has failed to include representative unfavorable data" and supports this contention by citing Fitzsimmons *et al.*, "Low-amplitude, Low-frequency Electrical Field-stimulated Bone Cell Proliferation May in Part be Mediated by Increased IGF-II Release." The experiment concludes that changes in output parameters can adversely affect bone cell proliferation. As K&S knows very well, this is not adverse information. As noted above, the issue pertinent to the petition is whether the Non-invasive Bone Growth Stimulator can be safe and effective, and whether those that are not can be identified prior to marketing using the controls available to Class II.

K&S goes further by citing Fredericks etc., "Effects of Pulsed Electromagnetic Fields on Bone Healing in a Rabbit Tibial Osteotomy Model." The article itself describes an

animal study of a modified dosing regimen for a PMA-approved device. The device was effective in the rabbit model. This, of course, is not unfavorable by any standard. Then, K&S contends that a device with the same output parameters "did not work clinically." But there is no published article describing this purported clinical failure, and there were no details provided by K&S to show how it was concluded, if indeed it was ever concluded, that the same output parameters failed in humans. Judging from it assertion, K&S must believe reclassification petitions must contain information unavailable to the public; a requirement, of course, that no applicant can meet. Moreover, K&S must believe that unsubstantiated assertions made by financially conflicted parties should have weight in the Agency's deliberations. K&S and its clients are conflicted, and did not provide important facts, such as whether output parameters were translated properly from the animal to human model, whether the human study matched the long bone use in the animal model, and how the "did not work" assessment was established (number of subjects, condition of the subject, criteria for success or failure, subject compliance, and follow-up time).

A number of physicians and scientists, e.g., Jon Zoltan, M.D., James Ryaby, Ph.D., John Bishop, M.D., Barton Sachs, M.D., and Raymond Linovitz, M.D., have expressed a concern that they would have less confidence in Non-invasive Bone Growth Stimulators if they did not undergo premarket approval. There is a consistency in their letters which suggest that that their comments may have been prompted more by the manufacturers that hold PMAs for these devices than by public health considerations. In addition, RS Medical believes that persons providing comments should reveal whether they have any financial interest in the matter under review in order for FDA to consider the dependability and importance of their comments; the comments did not include such information. In short, the comments suggest, at least in part, that the 510(k) program is itself unsafe and ineffective. On the other hand, RS Medical's opinion is that the 510(k) program is appropriate for any device when the controls available in Class II, including 510(k) notifications, are sufficient to ensure safety and effectiveness. If the individuals providing comments had demonstrated their knowledge of the controls available in Class II, their comments might have had some merit.

As explained above, prior to the discussion of what type of information is favorable and unfavorable to the petition, RS Medical has revisited the articles it uncovered in its original key-word search to determine if any excluded articles should be described and considered. It turns out that only 165 articles, not 166 as stated in the original petition, were considered as potentially applicable as a result of the original key-word search. This led to a detailed description of 41 of the 165 articles. Attachment I describes again the original search protocol and RS Medical's reassessment of its results. RS Medical found two additional articles, from the 165, which should have been included in the Agency's review. The results of these articles support the petition and are discussed in Attachment III.

RS Medical also conducted an additional key word search. Among other objectives, this search included an effort to identify any unsuccessful clinical study preceded by successful preclinical work. The search methodology is described in Attachment II.

Attachment III summarizes all the new findings, except the results of searches for "biological effects" and the "effects of fixation devices" which are discussed below in the answers to specific Agency points related to these subjects, and in specific attachments related to these points.

The preclinical work identified in the searches describes research in animal models and *in vitro* systems to investigate the safety and effectiveness of various output parameters. Positive effects regarding growth/repair and improved strength were observed, and negative effects regarding a lack of improvement in these characteristics were observed as a result of stimulation. Dose/Response studies were conducted to try new waveforms or determine which part of a waveform may be most effective. It is reasonable to conduct such studies to determine which signals would have the most potential clinically. Signals which are not effective in the preclinical animal testing would not be expected to proceed to clinical use. Indeed, these studies do not represent unfavorable information, but demonstrate the value of preclinical animal testing as outlined in the guidance. Abundant literature exists describing potential animal models for use in testing device output parameters and their effects in the stimulation of bone growth and repair. These studies only indicate that ineffective signals can be identified in animal trials and they emphasize the need for the careful choice of animal models employed and the careful execution of the mechanics of the study and care of the animals.

The preclinical work in cell culture systems is designed to examine the mechanism(s) of action of various electrical stimuli in bone repair processes and the types of cells that may be recruited or respond to the stimulus. There are efforts to determine: the sequence of events which occurs as a result of electrical stimulation; the interaction of the fields at the level of the cell membrane with regard to ion channels and receptor interaction; signal transduction; growth factor production/regulation; and, cell types that respond and those that do not. This body of work represents a continuing effort in the study of cell biology and the effects of internal and external electrical and electromagnetic effects. This type of testing is included in the preclinical analysis and testing section of the proposed guidance document. Unsuccessful studies in these animal, organ, or cell culture system models are not unfavorable to the petition, but reflect expansion of the knowledge base related to the mechanisms involved and the potential effectiveness of proposed output parameters.

With regard to the clinical experience, an additional 133 subjects are described for both nonunions and indications not related to the reclassification effort. Four of the studies are randomized controlled studies with two of these studies actually related to the indications which are proposed for-reclassification (Barker et al., 1984 and Dunn and Rush, 1984). None of the studies represent large populations, but are similar to those reports presented in the original petition. The various treatment sites and types of nonunions and fractures are similar, as well as the descriptions of definitions of success. Effectiveness is based upon radiographic and clinical evaluation, although details presented in the reports vary with regard to these assessments. Overall, the success rates for achieving union are similar to those reported and discussed in the original petition. The rates of successful union range from 72.2% to 90% in these

reports. PEMF was also shown to be similar in effectiveness to direct current stimulators in the randomized controlled study above. Only one article **might be construed** as unfavorable. It is the study of tibial nonunions in which PEMF treatment did not exhibit enhanced unions as compared to controls (Barker et al., 1984), which is widely referenced as evidence of the possible ineffectiveness of PEMF. This study is equivocal and neither the device nor the related preclinical testing was identified. A lack of safety or effectiveness in clinical trials is not in any way unfavorable to the petition unless such findings directly relate to an existing approved Non-invasive Bone Growth Stimulator, or to a device which performed well in all preclinical tests and then failed in properly translated human studies (signal adjusted for human use). The petition has stated that there is a risk of ineffective output parameters associated with the device. The output parameters in this case may have been ineffective or the population not large enough to make a clear assessment. Certainly, the larger body of publicly reported clinical experience demonstrates different results than this single report.

2. The petition appears to suggest that subsequent to the reclassification of non-invasive bone growth stimulators your proposed device would be "exempt from 510(k) requirements" (pg 89-90) (i.e. not require a 510(k) marketing submission). This is not acceptable. You do not currently own a legally marketed bone growth stimulator PMA device or a Pre-amendment device. Therefore, the submitted petition is considered to be a citizen's petition for the reclassification of the product group and NOT your proposed device. If the reclassification is granted, RS Medical must submit a 510(k) and receive a substantially equivalent determination prior to marketing your device.

Response: RS Medical intends to respond to this item at a later time. We believe the response to this matter is not related to whether the petition presents the information needed to reclassify the Non-invasive Bone Growth Stimulator. It only relates to how RS Medical may obtain marketing clearance for its device.

3. The 33 literature articles submitted to support the indication for use, "Treatment of established non-unions acquired secondary to trauma," includes 5 Capacitive Coupling (CC) and 28 Pulsed Electromagnetic Field (PEMF) studies. The petition does not appear to include valid scientific evidence to support the use of Combined Magnetic Field (CMF) devices for the treatment of established non-unions. Additional scientific evidence should be provided to support the use of CMF devices for this indication for use.

Response: RS Medical has elected to remove the technology of Combined Magnetic Field (CMF) devices from the reclassification petition. The petition now seeks to reclassify Non-invasive Bone Growth Stimulators based upon either the capacitive coupling or the pulsed electromagnetic field technologies. The literature reports extensively on both of the technologies for the treatment of established non-unions whereas only one article, which was not published in a peer-reviewed journal, addressed the effectiveness of the CMF-based devices. (Please refer to Section VI (B)(3) of the reclassification petition for this one article.)

4. The petition's risk analysis identified four general categories of health risk to the patient; electric shock, burn, skin irritation/allergic reaction, and inconsistent or ineffective treatment. The petition's risk analysis does not appear to adequately assess the risk of harm to the patient from the presence of metallic and/or electrical implants (including cardiac pacemakers, neurostimulators, and internal/external fixation). In addition, the petition's risk analysis does not appear to address risk associated with electrical stimulation at the biologic level, including carcinogenicity, mutagenicity, cell toxicity, and teratological effects. The risk analysis should be revised to include these risks.

Response: RS Medical agrees that the petition should address the risks identified in this point to consider. A discussion of each potential risk follows, including the identification of General and Special Controls to mitigate the risk. The proposed General and Special Controls to mitigate these risks are commonly applied to many medical devices. The risk analysis provided in the guidance document has been updated to include these risks and how they will be mitigated.

Potential Harm to Patients with Electrical Implants – RS Medical agrees that a Non-invasive Bone Growth Stimulator could theoretically have an adverse effect on the performance of an electrical implant, such as a cardiac pacemaker, cardiodefibrillator and neurostimulator. (The issue concerning internal/external fixation devices is discussed separately in this response.) RS Medical recommends that the risk to patients with an electrical implant, such as a cardiac pacemaker, cardiodefibrillator or neurostimulator, be mitigated by the application of the following two Special Controls:

1) adequate device labeling (21 CFR § 809), and
2) verification and/or validation testing (21 CFR § 820.30).

RS Medical recommends that the labeling for a Non-invasive Bone Growth Stimulator incorporate a warning which states that electrical implants, such as pacemakers, cardiodefibrillators and neurostimulators, may be adversely affected by the use of the stimulator. The proposed guidance document describes this Special Control. The commercially available devices incorporate such warnings in their device labeling. For new devices, this labeling requirement could be imposed during the review of 510(k)s.

If a specific manufacturer wishes to eliminate this warning from its labeling requirement, it should provide verification and/or validation testing (21 CFR § 820.3) in a 510(k) application to demonstrate that its specific device does not adversely affect the electrical implant.

Internal/External Fixation Devices – RS Medical presumes the Agency raised this issue because of the concern that the presence of an implant at the treatment site (either an internal or external fixation device) could adversely impact the delivery of an effective signal. Based on a review of literature, and on understanding of the CC

and PEMF technologies, RS Medical has concluded that neither a CC nor PEMF Non-invasive Bone Growth Stimulator is adversely affected in the presence of a non-magnetic, metallic fixation device. Also, a CC Non-invasive Bone Growth Stimulator is not adversely affected in the presence of a magnetic, metal fixation device, whereas a PEMF device can be. Thus, PEMF devices should have appropriate related precautions. These conclusions are drawn from the following information.

RS Medical reexamined the literature provided in Sections VI and VII of the original petition to evaluate the potential impact of fixation devices on device effectiveness. For the nonunion studies, the literature summary provided in the petition described the study populations with the following clinical information when available:

- location of the nonunion,
- percentage of subjects with previous treatment,
- mean number of previous treatments,
- number of subjects with concomitant surgery,
- length of time between fracture and stimulation treatment, and
- length of the follow-up.

RS Medical has now augmented this summary by describing the use of fixation devices in the study populations. Attachment IV provides the revised tables. The summary information now includes:

- number of subjects with fixation,
- type of fixation used, and
- impact of fixation on effectiveness (reported as either a rate or general conclusion),

The vast majority of subjects enrolled in the nonunion studies had undergone previous treatments for their condition, often including surgical treatments and the use of fixation devices (internal and external fixation devices). Overall, the Non-invasive Bone Growth Stimulator was found to be an effective treatment for patients with nonunions in the presence or absence of fixation devices. For example, the healing rates for nonunions treated with capacitive coupling devices were not affected by the presence or absence of metal fixation devices at the fracture site (Abeed 1988, Brighton and Pollack 1985, and Brighton et al. 1995). The results of the Scott and King study showed that nonunions treated with both capacitive coupling and fixation devices healed, whereas nonunions in the sham stimulation group did not heal (1994).

Tibial nonunions treated with PEMF devices also demonstrated that metallic fixation devices did not have an impact on the healing or success rate (Bassett 1981, Gossling et al. 1992, Ito and Shirai 2001). Colson et al. reported that, of the 19 subjects treated with PEMF devices and internal fixation for fractures of long bones and others, all achieved a successful union (1988). Several other studies also concluded that the presence of fixation devices did not adversely impact healing rates for nonunions treated with PEMF devices (Hinsenkamp et al. 1985, Simonis et al. 1984, and DeHaas et al. 1986). The additional literature searches conducted for this response identified a study by Bassett et al. that specifically addressed the issue of the effectiveness of PEMF devices in the presence of internal and external fixation devices (1982). This clinical study evaluated the effectiveness of a PEMF device for 540 nonunions. All subjects treated with PEMF stimulators had a history of nonunion after the use of plates, screws, rods or pins. No subject had concomitant surgery for the nonunion during the study. The overall success rate for these subjects was 75%, and ranged from 86% for the tibia to 60% for the humerus.

Contrary to these authors' findings, Madroñero et al. found that none of the four subjects treated with metallic fixation devices and PEMF Non-invasive Bone Growth Stimulators achieved a successful union (1988). Bassett provides further commentary on considerations for the compatibility of fixation devices and PEMF stimulators (the magnetic field set up by magnetic fixation devices does not interfere with the signal produced by CC devices). He states that the presence of metallic fixation devices could theoretically impact the field distribution of the PEMF device (1977). The distinction to be made when detailing the use of metallic fixation devices with Non-invasive Bone Growth Stimulators, however, is the material of the fixation device. Bassett explains that compatibility can be established between the PEMF devices and metallic internal fixation devices if the material of the fixation device is **non-magnetic** (Bassett 1978). Bassett adds that many of the plates, screws, and rods used for fixation are constructed from non-magnetic materials, such as stainless steel or cobalt-chrome alloys, which do not adversely impact the healing rates for nonunions. For this reason, the current, commercially available PEMF devices provide a precaution to this fact in their labeling.

RS Medical has also reassessed the original literature to determine whether the Non-invasive Bone Growth Stimulator works in the presence of hardware or instrumentation when used as an adjunct for the lumbar spinal fusions. (Please refer to Attachment IV.) Many of the studies showed no significant difference when Non-invasive Bone Growth Stimulators were used in the presence or absence of fixation devices for spinal fusion (Mooney 1990, Jenis et al. 1990, and Simmons et al. 2004). The Bose study demonstrated a fusion success rate of 97% when lumbar fusions were treated with a combination of internal fixation and PEMF stimulation (2001). Further, those clinical studies which compared the Non-invasive Bone Growth Stimulator to a sham stimulation demonstrated the overall benefits of the stimulation in study populations in which the majority of subjects had internal fixation. The Goodwin et al. 1999 study showed a fusion success rate of 81.5% for active subjects compared to 61% of the sham stimulation group. In this study 77% of the active

subjects and 82% of the sham stimulation subjects had internal fixation. The Mooney study demonstrated rates of 91.7% for active subjects versus 71.8% for the sham stimulation subjects (1990). In this study, 75% of the active subjects and 74% of the sham actives had internal fixation.

The literature review demonstrates that the Non-invasive Bone Growth Stimulator remains effective in presence of fixation devices with one possible exception concerning the combined use of a magnetic fixation device and PEMF stimulator. RS Medical recommends the labeling of a Non-invasive Bone Growth Stimulator employing PEMF technology incorporate a warning or precaution that magnetic fixation devices may interfere with the delivery of an effective treatment to the patient as a Special Control. The proposed guidance document details this Special Control.

Risk Associated with Electrical Stimulation at the Biologic Level - Citations obtained from the original reclassification petition literature search as well as new literature searches were reviewed to assess the incidence of possible biological effects, including carcinogenicity, genotoxicity, mutagenicity, and teratogenicity. Details of the search and a discussion of the results are presented in Attachment V. A discussion of the specific articles pertinent to this reclassification effort are provided here.

Carcinogenicity, Genotoxicity, and Mutagenicity

Over the past several decades, there has been concern regarding the possible relationship between exposure to electromagnetic fields and adverse biological effects, such as cancer development. Concern has been expressed about exposure to electrical energy /electromagnetic radiation from sources such as power distribution and transmission lines (extremely low frequency [ELF] 50Hz magnetic fields), as well as from occupational sources (navigation and surveillance equipment), household wiring, microwaves, and communication devices. The potential for genotoxicity and mutagenicity has been studied and reported extensively in the literature. From the overall information, solid evidence does not exist establishing a clear link between exposure to these sources and cancer in humans.

The majority of the research involves frequencies associated with common environmental electromagnetic exposures (power lines, communications devices, and R.F.s, and microwaves). It should be noted, however, that the therapeutic PEMF frequencies which are the subject of this reclassification petition differ substantially from these. PEMFs are intended to simulate a range of frequencies which occur naturally in the body. Thus, the bulk of the available literature does not specifically pertain to these fields. One reference reports data specific to frequencies related to bone growth stimulators (Jacobson-Kram, 1997). The relevance of available biological safety research as it relates to frequencies produced by bone growth stimulators is also discussed by Bassett (1989). One must also consider the apparent lack of published clinical evidence reporting this type of adverse event. The evidence

suggests that this type of electromagnetic energy /clinical exposure does not have adverse biological effects.

Published work on the Orthofix implantable bone growth stimulator (AME implantable stimulator) and a developmental PEMF signal is of particular interest, considering this reclassification petition (Jacobson-Kram et al., 1997). The mutagenic potential of the electric and electromagnetic fields elicited by this device at clinical and supra clinical doses was evaluated in the Ames test, CHO chromosomal aberration assay, cell transformation assay, and unscheduled DNA synthesis. Initial and independent repeat studies were conducted and compared to untreated controls and positive controls. The pulsed electric field consisted of a burst of 99 pulses, at a repetition rate of 1.5 pulse bursts per second. The low dose cultures were exposed to a signal 3mV/cm positive amplitude and 1mV/cm negative amplitude. High doses were 10 times the amplitude of the clinical device. The electromagnetic fields mimicked an Orthofix developmental PEMF signal (burst of 1609 pulses, repetition rate of 1.5 pulse bursts per second, positive portion 4 μs wide and negative portion 12 μs wide). The positive amplitude was 9 Tesla/second and the negative amplitude was 3 Tesla/second which is the same as the therapeutic device. Again, cultures were also exposed to doses with 10 times these amplitudes and compared to untreated controls.

Evidence from these studies did not indicate that such electrical and electromagnetic exposures caused genetic damage as measured by the Ames test, In vitro chromosomal aberration assay, transformation of BALB/3T3 cells, or unscheduled DNA synthesis in rat hepatocytes. Neither the implantable stimulator output (both doses) nor the high frequency PEMF signal (both doses) caused an increase in revertants per plate. They were similar to untreated controls. There was no sign of cell toxicity or mutagenic activity. An increased frequency of chromosomal aberrations or mitotic index in CHO cells was not observed with either treatment. Cell transformation and cloning efficiency were not affected by these signals either. Measurable toxicity, as measured by unscheduled DNA synthesis in rat hepatocytes, was not observed by either signal at any dose level. Positive controls in all assays elicited the appropriate positive responses. These signals are not mutagenic nor clastogenic in these assays. The fields also did not increase cell transformation or unscheduled DNA synthesis. This report provides additional evidence that electric and electromagnetic fields do not appear to present a genetic hazard, adding to the preponderance of existing literature on environmental exposures showing negative effects in these assays.

Bassett summarized the safety concerns of the use of PEMFs as well (1989). He noted that the PEMF energetics differ substantially from those of power lines, radiofrequency, and microwaves in that PEMFs were designed to simulate naturally occurring stress-generated electric responses. As such, PEMFs contain a selected range of frequencies and amplitudes well within the range normally presented in the body. PEMFs are asymmetric and broadband. Predominant frequencies are at the very low end of the electromagnetic spectrum. Thus, the overwhelming amount of studies reported using other exposures do not necessarily apply to the frequencies

which are the subject of this petition. There does not appear to be evidence suggesting that these frequencies initiate the cancer process. Bassett describes a sarcoma model in Swiss-Webster mice which has been used as a safety screening test for new waveforms. Survival and spontaneous tumor formation in these mice exposed continuously to PEMF waveforms did not differ from the unexposed control animals. The PEMF did not have any effect on the tumor progress. A different model in Balb/C mice actually showed significant decreases in tumors treated with PEMFs – indicating a beneficial effect in this model. The PEMF-treated tumor cells also exhibited a more normal complement and distribution of intracellular structures and organelles.

Bassett also notes that overall clinical experience as reported in the existing literature does not appear to suggest a relationship between these waveforms used clinically and carcinogenesis or genotoxicity. There has not been an increase in case reports noting an increase or exacerbation of tumors in PEMF-treated patients. He reports on up to 10 years experience in treating pathological nonunions in bone cancer patients. PEMF may produce bony union in these patients, but no evidence of the malignant process recurring was observed. He does report that colleagues report on 2 patients who suffered recurrence of malignancy after PEMF treatment, however, a literature report is not cited and pulse characteristics not described. Reviews of the literature for the original petition and this amendment are not populated by case reports or clinical evidence giving reason for concern relative to an increased cancer risk. It is prudent, however, to continue to monitor the evidence during the continued clinical experience.

Teratology

There does not appear to be evidence linking clinically used PEMFs to congenital malformations. Nishikawa investigated the effects of the Bi-Osteogen system (Electrobiology) (5msec positive going burst with a repetition rate of 15Hz) on pregnant mice. Three experiments were conducted in pregnant mice that were exposed to PEMFs. Mice were exposed for 8 hours/day between the 6^{th} and 15^{th} day of gestation in the first experiment. In the second and third experiments, mice were exposed for 24 hours/day between 0 and 18 days of gestation. Field strength and induced voltage was determined on each floor of the housing unit. Upon sacrifice, fetuses from the first two experiments were examined for external, visceral, and skeletal anomalies. In the third experiment, the offspring were examined for behavioral development. A significant increase in the body weight of offspring was observed between 8 and 21 days, with a transient acceleration of behavioral effects. However, no detrimental effects were observed on the pregnancy or prenatal and postnatal development (Nishikawa, 1987).

Bassett also addressed the issue of teratogenesis (1989), citing the existing studies in chick embryos noted by Juutilainen in a comprehensive review article (2005, see Attachment 5). Malformations in embryogenesis reported could not be successfully reproduced despite careful design and control of exposure conditions. A thermal

effect could not be ruled out. Some general growth of skeletal tissues was noted in birds, but no adverse effects on embryogenesis or development in mammals. A PEMF generator which produced pulses different than those in clinical use was reported to affect male scent-marking behavior and gonad size in rats. Exposure patterns were also different than those clinically employed. In another extensive study, four successive generations of mice were exposed to basic pulse patterns for 24 hours per day. No abnormalities in mating, gestation, delivery, litter size, animal weights, behavior, development, or re-mating were observed. Neither were abnormalities of organs revealed at the termination of continuous exposure experiments. These results were confirmed in additional safety experiments conducted by independent commercial laboratories to support commercial applications. Furthermore, Bassett cites clinical experience in over 600 female patients at the time of the review documented in detailed questionnaires. This population exhibited similar data on menses, menopause, and pregnancy as the remaining female population at he time. The current literature does not suggest issues related to these types of adverse events given the clinical use of bone growth stimulators over the past 25 years.

Although not a teratology study specifically, limb regeneration of newts in response to PEMF stimulation was also studied (Landesman and Douglas, 1990). This reference appeared in the original petition bibliography. Bilateral amputations were performed on adult newts. The control group was compared with a group receiving continuous PEMF exposure (Bi-Osteogen System 204, ElectroBiology, Inc.) for 30 days, except for 30-minute feeding/watering periods twice weekly. The waveform was described as: 200 μsec pulse width, 28 μsec negative width, 5 msec pulse burst width with 61.24 msec between bursts. Both groups were maintained under identical conditions for an additional 3-4 months. Skeletal analysis was conducted on control and PEMF regenerated limbs and compared to a native group of newts. It is noted that regenerated forelimbs typically exhibit some variations in the digit and carpal bones, even without intervention. Normal regeneration does not always result in exact duplication of the previous limb in various newt species. PEMF neither accelerated nor inhibited limb regeneration. Developmental milestones and histological analysis were not affected by exposure to PEMF. There was a decreased number of forelimbs with a normal skeletal pattern (60%) compared to 98% in the native group and 72% in the control group. Both the control and PEMF group showed the same degree of abnormalities, however. There were 29/240 PEMF-exposed limbs that showed unique gross defects (loss of digits and carpals, absence of more than one digit, excessive number of carpals, fusion of carpals, defects in the distal ends of the radius and ulna.). These types of defects have been noted also following repeated amputation and other stimuli and a common mechanism is not known.

Conclusions

Overall, the range of frequencies and exposures studied most often focus on those outside the range of interest in this petition. In the absence of a thermal effect, the effects of the fields are generally negative. It is noteworthy that the available

comprehensive reviews of the literature conclude that the environmental and medical exposure ranges do not appear to be genotoxic or mutagenic and long-term bioassays also produce negative results overall. Specific information pertaining to the fields similar to those of interest in the petition also suggests negative results with respect to standard genotoxicity assays (Jacobson-Kram et al 1997). The available discussion related to the safety of PEMFs reinforces this. While the data are by no means fully conclusive, the evidence points to lack of genotoxic, carcinogenic, and teratologic potential of the subject waveforms.

Special Controls can also be utilized and have been proposed to address any potential risks. Appropriate warning language can be used. Incorporation of a warning is proposed that the long-term effects of electrical and magnetic fields have not been studied in humans. Furthermore, it should be stated that the safety and effectiveness in pregnancy have not been studied. Effects of the device on mothers and the developing fetus are not known. Anyone who is pregnant or intending to become pregnant should be referred to her physician prior to treatment. (See the precautions in the proposed guidance document in Attachment VI.)

5. The petition has identified thermal burns as a potential risk associated with this device. The petition has also recognized that the majority of burn-related, adverse events occur while the patient is using and recharging the device during sleep. To mitigate this risk the petition proposes appropriate warning labeling. Considering that treatment may be prescribed for up to 14 hrs per day, this mitigation may not be reasonable as a patient may not have the time to adequately charge and use the device during their wakeful hours. The petition should be revaluated to provide further mitigating activities to minimize the risk of thermal burns to the patient.

Response: RS Medical agrees with the Agency's suggestions. In addition to having appropriate instructions for use which include a description of safe procedures for recharging, and any appropriate warning statement about the risk of using and charging the device at the same time, the device can be designed to eliminate or greatly mitigate the risk. The device can be designed so that batteries cannot be charged while the device is in use. This approach provides an effective safety precaution; but, when used by itself, it can lead to circumstances where the patient does not have a device available for use when needed, i.e., the patient may not have charged the batteries sufficiently prior to wanting to use the device. To solve this problem, the device can be designed so that the battery pack must be removed from the device for charging; and, at least two usable battery packs can provided with the device, allowing one fully charged pack to always be available for use. Such a design is no different than the designs used for a multitude of consumer products that are used by patients on a routine basis, e.g., household tools, and cameras. Other designs might also be used to address the issue.

We have modified our proposed guidance document to address this issue (Attachment VI). The guidance document advises applicants seeking 510(k) clearance for new

devices of this type to address how this risk is being mitigated by design safeguards and/or labeling instructions and warnings.

The industry will not need to be convinced to move toward this, or other design enhancements. Manufacturers must do so in order to remain competitive; and, given the lower regulatory burden associated with changes to Class II devices, such incremental enhancements are more likely to be made if this device is reclassified.

6. The proposed special controls appear to outline a general set of output waveforms (burst length, pulse amplitude, pulse amplitude, and frequency) upon which substantial equivalence might be established. However, it is unclear if these parameters are adequate, in themselves, to assure safety and effectiveness. These device waveform parameters do not appear to provide a complete set of technical parameters which would be sufficient to assure the reproducibility of clinically effective treatment. The parameters do not address the distribution of the induced magnetic/electric fields, coil geometry, effective dosimetry of the resulting electrical gradient/magnetic field (magnetic field mapping), material and dimensions of the electrodes (capacitive plates), pulse rise/fall time, pulse width/shape, symmetry/asymmetry of waveform, and other technical parameters. In addition, the petition should include rationale to justify how the proposed technical specifications are sufficient to validate an effective clinical treatment signal. The petition should be revised to address what range of technical specification is necessary to ensure a clinically effective treatment signal/dose.

Response: There are multiple components to consider in this point.

First, the Agency notes that the petition appears to outline a general set of output waveform characteristics which by themselves are not adequate to establish the substantial equivalence of new devices of this type; i.e., burst length, pulse amplitude, pulse amplitude, and frequency are not by themselves adequate to fully describe the technological specifications of a new device for purposes of comparison to a predicate. The Agency's observation may have resulted from a miscommunication on the part of RS Medical. Specifically, the original petition identified in several places these limited characteristics and specifications as important features of the device. For example, Table 1 in the proposed guidance document lists these characteristics and specifications by themselves. But, the Device Description section, and the Preclinical Analysis and Testing section, which follow Table 1, identify all of the characteristics mentioned by the Agency in Point #6; i.e., these sections include the distribution of the induced magnetic/electric fields, coil geometry, effective dosimetry of the resulting electrical gradient/magnetic field (magnetic field mapping), material and dimensions of the electrodes (capacitive plates), pulse rise/fall time, pulse width/shape, and symmetry/asymmetry of waveform. Indeed, these sections of the proposed guidance document state that a 510(k) applicant should provide more than the items identified in Point #6. RS Medical has revised the proposed guidance document in an effort to eliminate the

confusion caused by Table 1 (see Attachment VI for the modified guidance document).

To further clarify the matter, RS Medical is providing below an inventory of the descriptive information and performance testing data needed to fully understand the technological characteristics and specifications of a device of this type. The inventory consists mainly of items included in the original guidance document. It also includes some additional items and some clarifications, which also appear in the enclosed guidance document. (Attachment VI provides the revised guidance, and Attachment VII provides a red-lined version of the original guidance to show how the original version has been modified.)

The original proposed guidance document first specified that the manufacturer provide a general description of the output waveform generator and accessories; so does the revised guidance document. Specifically, it requests the information summarized below (see page 6 of the guidance document):

- A complete description of the output waveform generator and its power source, including its dimensions, weight and materials (supplemented with pictures and/or engineering diagrams)
- A complete description of the user controls, display functions and alarms
- A description of the connections of the electrodes or coils to the generator and to the patient (including the use of any positioning guides or blocks)
- Identification of each electrode or coil recommended for use, and its intended anatomical location, orientation, and positioning guides or block (if applicable)
- A comparison table for substantial equivalency purposes
- Accessories (page 7 of the proposed guidance document)[10]
- Electrodes – A description of the type and size of the recommended electrodes, including dimensions, surface area, materials and configuration of the leads and electrodes. This includes a description of the attachment of the leads and electrodes to the patient. This description should be supplemented with pictures and/or engineering diagrams.
- Electrode Lead Wires and Patient Cables – A complete description of the wires and cables, including lengths, constructions, materials and connections, and compliance with the mandatory performance standard (21 CFR § 898).

[10] The proposed guidance document also addresses the information recommended for accessories, such as electrode conductive medium, batteries, battery charger, and physician test meter.

This description should be supplemented with pictures and/or engineering diagrams.

- Coils and Positioning Accessories – A complete description of the recommended coils, including type, size, materials, geometry, configuration, number of turns and windings, and method of attachment to the patient including any positioning devices (guides or blocks). This description should be supplemented with pictures and/or engineering diagrams.

Thus, the guidance document requests a full description of the device's **technological characteristics**. This, in turn, allows the Agency to determine what **technological specifications** need to be described, and what testing must be done to ensure that the technical specifications are met.[11] The proposed guidance document describes the required information on technological specifications and testing in Section 7 – Preclinical Analysis and Testing. Specifically, the proposed guidance document recommends that the following be provided for capacitive coupling and PEMF devices:

For capacitive coupling devices:

- A minimum of four oscilloscope tracings of the output waveform (with appropriate electrode connected) under loads through the range of operation (e.g., 200-700 Ω) should be presented as voltage versus time. If the generator is capable of producing more than one waveform type and/or can be used with electrodes of more than one type or size, an oscilloscope tracing of each waveform/electrode combination should be submitted. In addition to quantitatively identifying all salient features of the voltage and time variables, the horizontal and vertical oscilloscope gain settings should be specified. The procedure for making the waveform measurements should be described.
- Maximum output current
- Maximum and RMS output voltage
- Whether the signal is constant current or constant voltage
- Open circuit detection range
- Waveform shape and description
- Waveform frequency

[11] The terms "technological characteristics" and "technological specifications" have different meanings, as described below in further answer to this point to consider.

- Spectral analysis to determine the extent and/or existence of a 2nd order harmonic frequency and its strength (such testing may need to be performed in an isolation chamber)
- Current density at the electrode/skin interface (for each waveform / electrode combination)
- Indicate the estimated current density and/or electric field strength at the treatment site.
- Power density at the electrode/skin interface (for each waveform / electrode combination)
- Charge per pulse and charge density at the electrode/skin interface (for each waveform / electrode combination)
- Estimated current density at the treatment target site
- Recommended duration of use per day
- Provide a diagram of the output waveform with all stimulation parameters and temporal characteristics clearly labeled to supplement the oscilloscope tracings. In conjunction with this diagram, provide a table that summarizes the output specifications, with each specification listed as an acceptable range or as a single value ± tolerance.
- Provide an equivalent circuit diagram for the output generator and all electrodes, noting all impedance values.
- Describe the method of attaching the leads and electrodes to the patient. Describe the placement of the anode(s) and cathode(s) relative to each other, relative to the treatment site, and relative to surrounding structures and excitable tissues (e.g., heart, peripheral nerves, spinal nerves, etc.).
- Compare the information described above with the same information for the predicate device.

Attachment XI provides a technical report prepared for the RS Medical engineering team. It describes the testing of seven commercially available capacitive coupling Non-invasive Bone Growth Stimulator devices (4 – SpinalPak II® devices, 2 – SpinalPak® devices and 1- OrthoPak® device). The output waveform, fundamental frequency, voltage, current and spectrum analysis produced by each device were quantified for each device at various environmental conditions, resistance levels and battery levels. Scope pictures and data summaries for the tests are included in the report.

Attachment XII provides a technical report prepared for the RS Medical Engineering team. It describes the normalized current distribution for the EBI Soft-Touch™ Electrodes. An analysis was completed for the electrodes that were manufactured by LECTEC (type used with the original SpinalPak device) and for the electrodes manufactured by Uni-Patch (currently used with the SpinalPak system). The construction and component parts were identified and electrical tests were completed along with current distribution maps.

The information required for PEMF devices are shown below:

- Provide oscilloscope waveforms of the magnetic fields and of the time rate of change of the dynamic magnetic field (i.e., dB/dt) corresponding to one complete cycle of the output signal. The measurements should be made with the magnetic field probe (e.g., detector coil) located in a region representative of the center of the treatment target area.

- Provide diagrams of the output waveforms with all parameters and temporal characteristics clearly labeled to supplement the oscilloscope tracings. In conjunction with the diagrams, provide a table that summarizes the output specifications, with each specification listed as an acceptable range or as a single value ± tolerance. This should include the following: burst period, number of pulse pairs in a burst, average amplitude of pulse 1, average amplitude of pulse 2, rise time for pulse 1, rise time for pulse 2, duration of pulse 1 and duration of pulse 2.

- Provide a complete mapping (i.e., throughout the entire treatment target area) which characterizes the magnetic field, and dB/dt, averaged over the duration of the primary pulse. Specifically, for each coil and for each coil position, present three-dimensional mapping data which show the measured values at each location. A sufficient number of locations should be used to adequately describe the fields throughout the entire treatment target area. Spatial intervals of no greater than 2 cm are recommended.

- Describe the methodologies used to obtain the waveforms and field maps. Include a complete description of the instrumentation, calibration procedures, and conversion factors used in the acquisition and presentation of data, and specify the physical dimensions, number of turns, winding arrangement and spatial resolution of the detector coil.

- Provide spectral analyses to characterize the frequency content of the signal delivered through each coil. Identify the gain setting and bandwidth for each plot and describe the methods and instrumentation used to obtain the data.

- Describe the type, size, materials, geometry, configuration, number of turns and the winding arrangement of each coil, and provide a description of the electrical characteristics of the transmitting coil including the resistance, inductance and capacitance (where applicable).

- Provide the recommended hours of use per day.
- Compare the information described above with the same information for the predicate device.

Attachment XIII provides another report prepared for the RS Medical engineering team. This report lists measurements and calculations associated with the technological specifications of the magnetic field patterns and waveforms of two different PEMF devices. It identifies such items as the burst period, number of pulse pairs in a burst, the average dB/dt of pulse 1, the average dB/dt of pulse 2, the duration of pulse 1, the duration of pulse 2, the magnetic field at the center of the coil, the coil composition, the geometry of the coil, the number of turns in the coil, and the magnetic field pattern, amongst other measurements and calculations.

The reports described above establish several important facts. The reports provide evidence of what is already known to people in this field. Existing Non-invasive Bone Growth Stimulators can be tested to identify how they perform with respect to the technical characteristics that are important to their performance, i.e., testing of the devices can identify the specifications associated with a specific characteristic. These which allowed the device to be released for marketing. The testing of one device would generally not establish the nominal value for a given specification, but it indicates at least a value within the range of values accepted for the release of the product. The testing of several devices gives further information on the range of release specifications, and new devices can be produced to perform within those ranges.

RS Medical believes the device characteristics described above, combined with information and testing associated with the characteristics' technological specifications, are adequate for evaluating the substantial equivalence of new and predicate device. These reports are not intended to address all the required items. RS Medical intends to address all the items in the proposed guidance document in order to fully describe the specific Non-invasive Bone Growth Stimulator it intends to market, but this information will be provided at a later time.

K&S had comments related to this matter, in which K&S asserts that RS Medical "...failed to define the waveform parameters that are necessary for the reproduction of waveforms with proven safety and effectiveness..." [Page 13.] To justify its assertion, K&S goes on to use only the limited parameters described in Table 1 (burst length, pulse amplitude, pulse amplitude, and frequency) to show when using these factors alone one could develop waveforms that would be significantly different in comparison to the devices proposed for reclassification. Numerous charts are provided to illustrate these unacceptable waveforms. K&S suggests that these vastly different waveforms could be submitted in a 510(k) and be found to be substantially equivalent if the Agency were to accept the proposed petition. [Page 18.]

This is unqualified nonsense. A mere casual, but complete, review of the proposed guidance document would have informed a reader that an applicant would need to

submit much more information about the waveform; information which would provide legitimate and complete comparisons between a new and predicate device.

K&S goes on to mix its argument that the information required in the guidance document is too vague with the argument that information about the potential predicate which is necessary for an adequate comparison is proprietary. Thus, adequate comparisons cannot be made. One could, of course, apply this contention to every type of device in which established predicate devices exhibit certain features that manufacturers consider proprietary. But, as everyone in the industry knows, obtaining such information is challenging but normally accomplished. This fact is illustrated by the reports provided above.

The point to consider also states:

In addition, the petition should include rationale to justify how the proposed technical specifications are sufficient to validate an effective clinical treatment signal.

Response: Before responding, RS Medical believes it will be useful to define certain terms. We use the term "characteristic," and related forms of the word, to refer to a design feature of these devices, e.g., a pulsed signal and coil orientation are design features, or characteristics. Such characteristics need to have a "specification" which establishes a desired value for the characteristic, such as a quantified amplitude. A specification usually has a "nominal" discrete value, combined with a product "release" value or tolerance which is typically a range consisting of plus or minus values around the nominal value.

With this understanding of the meaning of these terms, RS Medical would like to clarify our petition. We did not mean to propose any specific "technical specifications" for the Non-invasive Bone Growth Stimulator.

Our proposed definition of the type of device is consistent with this intention. It describes some characteristics of the device, e.g., it mentions an output generator, but it does not describe "technical specifications" for the output generator.

RS Medical also provided a general description of the existing types of devices to be reclassified, and this description included gross technological specifications, i.e., as in Table 1. We did not mean to imply that all Non-invasive Bone Growth Stimulators should comply with these technical specifications. Indeed, we believe it is neither necessary to describe all of the technological "specifications" of the individual devices proposed for reclassification, nor that it is necessary to impose, by regulation, any technological specifications on the specific devices within this type in order to reclassify them into Class II.

RS Medical does not believe technical specifications need to be set for the existing devices because enough is known about the safety and effectiveness of these devices to make the setting of technical specifications unnecessary. This is not to say that the

petition does, or needs to, establish that each specific device which will be reclassified is safe and effective, as is done in a PMA. Nevertheless, there is a compelling body of publicly available evidence contained within the petition which establishes that the existing devices are "safe and effective," as that term is meant to be used in the "classification" sense.

The concept that the term "safe and effective" has a different meaning in the "PMA sense" than in the "classification sense" is illustrated in FDA's classification regulation. This regulation applies the term "safety and effectiveness" to a number of different situations. In doing so, the regulation, in conjunction with FDA practices, and the pure logic of the matter, establish that there are different levels of documentation and assurance associated with a determination of the safety and effectiveness of a device, or type of device, depending on circumstances. Section 860.7(b) of FDA classification's regulation states:

> In determining the **safety and effectiveness** of a device for purposes of classification, establishment of performance standards for class II devices, and premarket approval of class III devices, the Commissioner and the classification panels will consider the following, among other relevant factors: [Bolding added.]

The regulation goes on to describe various types of information that may be considered valid scientific evidence.

FDA has been directed to apply to the various types of devices only those regulatory controls that are needed to ensure the device's safety and effectiveness; with Class III and its associated assessment of safety and effectiveness in the premarket approval process being the strictest of those controls. The above citation from FDA's classification regulation, however, establishes that the classification process also involves an assessment of safety and effectiveness. But, if FDA had, during the process of classification, evaluated the safety and effectiveness of the devices it has put into Class II in the same way it evaluates the safety and effectiveness of the devices it subjects to premarket approval, the statutory framework for the regulation of devices would make no sense whatever. Under such circumstances, all individual brand name Class II devices would have been subjected to premarket approval prior to not being subject to premarket approval - - which makes no sense.

Thus, in order to classify, or reclassify, a device into Class II, FDA need not have PMA-like evidence, or PMA-like documentation, of the safety and effectiveness of the devices within the type of device under consideration.

Section VII of the original petition, entitled "Safety and Effectiveness of the Devices to Be Reclassified," presents information related to the safety and effectiveness of the specific devices proposed for reclassification. This information is not equivalent to what would be needed in a PMA, but it is compelling evidence for reclassification

and establishes that the existing devices need not be subject to required technical specifications.

Also, technical specifications need not be set for potential new devices. The information needed to adequately describe the technological characteristics and related technological specifications of new and predicate devices are described above. A list of this information would also appear in the 510(k) guidance document. The 510(k) guidance document may be made a required special control in the classification regulation. Thus, this information can be required, and be used to compare new devices with existing devices. This information can be used, if necessary, to ensure that the release criteria associated with technological specifications are virtually the same as any selected predicate device. Thus, new devices will be as safe and effective as their predicate.

The point to consider also states:

The petition should be revised to address what range of technical specification is necessary to ensure a clinically effective treatment signal/dose.

Response: As just discussed, the petition does not suggest that technical specifications be set. Notwithstanding this, the Agency's point might be considered from the point of view of how closely a new device's technological characteristics and specifications must match those of a predicate device in order to ensure that the new device will perform as well as the predicate.

RS Medical believes, however, that this is not a question that needs to be answered in this petition, just as such questions are almost never answered during a classification process. Instead, applicants who submit 510(k)s must justify a determination of substantial equivalence.

In this case, an applicant can use well established laboratory techniques to compare the "release technological specifications" of his or her device with those of a predicate device. Such testing can be used to establish virtually the same release technical specifications. Thus, a new manufacturer can design a device that is virtually identical in characteristics and specification to a predicate. Such a device would clearly be substantially equivalent. Furthermore, if such strict adherence to existing characteristics and technological specifications were the only way to ensure substantial equivalence, this would not be an impediment to reclassification. There is no rule requiring that devices within a Class II type of device have different designs in order for the type of device to be in Class II.

This abstract hypothetical construct that a new device may need to exactly match a predicate in order for the Agency to know the new device is substantially equivalent, however, is only a hypothetical construct. In the event that a new device has characteristics or specifications that are somewhat different than its predicate, there are numerous measures that can be taken to determine if, or if not, the new device is

substantially equivalent. The presentation of such arguments, backed up when necessary by testing data ranging from bench test to clinical tests, is the essence of the 510(k) program.

RS Medical looks forward to further participation in the Agency's deliberations on this matter, and we are available to answer any questions that may arise.

Sincerely,

William Carroll / MD.

William Carroll
Vice President, Research and Development

Cc: S. Brown, C. Herzog, N. Ogden, M. Provost

Enclosures:
Attachment I - Reassessment of Original Literature Search
Attachment II - Description of New Literature Search (Preclinical and Clinical)
Attachment III - Preclinical and Clinical Findings
Attachment IV - Fixation Findings
Attachment V - Biological Search and Results
Attachment VI - Guidance Document
Attachment VII - Guidance Document (red-lined version)
Attachment VIII - Bibliography for Original 165 Articles
Attachment IX - Bibliography for Preclinical and Clinical Articles
Attachment X - Bibliography for Biological Articles
Attachment XI - Technical Report for Capacitive Coupling Devices
Attachment XII - Technical Report for Electrodes
Attachment XIII - Technical Report for PEMF Devices